Loss of mitochondrial functions associated with azole resistance in Candida glabrata results in enhanced virulence in mice.

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Résumé en anglais	Mitochondrial dysfunction is one of the possible mechanisms by which azole resistance can occur in Candida glabrata. Cells with mitochondrial DNA deficiency (so-called "petite mutants") upregulate ATP binding cassette (ABC) transporter genes and thus display increased resistance to azoles. Isolation of such C. glabrata mutants from patients receiving antifungal therapy or prophylaxis has been rarely reported. In this study, we characterized two sequential and related C. glabrata isolates recovered from the same patient undergoing azole therapy. The first isolate (BPY40) was azole susceptible (fluconazole MIC, 4 μg/ml), and the second (BPY41) was azole resistant (fluconazole MIC, >256 μg/ml). BPY41 exhibited mitochondrial dysfunction and upregulation of the ABC transporter genes C. glabrata CDR1 (CgCDR1), CgCDR2, and CgSNQ2. We next assessed whether mitochondrial dysfunction conferred a selective advantage during host infection by testing the virulence of BPY40 and BPY41 in mice. Surprisingly, even with in vitro growth deficiency compared to BPY40, BPY41 was more virulent (as judged by mortality and fungal tissue burden) than BPY40 in both systemic and vaginal murine infection models. The increased virulence of the petite mutant correlated with a drastic gain of fitness in mice compared to that of its parental isolate. To understand this unexpected feature, genome-wide changes in gene expression driven by the petite mutation were analyzed by use of microarrays during in vitro growth. Enrichment of specific biological processes (oxido-reductive metabolism and the stress response) was observed in BPY41, all of which was consistent with mitochondrial dysfunction. Finally, some genes involved in cell wall remodelling were upregulated in BPY41 compared to BPY40, which may partially explain the enhanced virulence of BPY41. In conclusion, this study shows for the first time that mitochondrial dysfunction selected in vivo under azole therapy, even if strongly affecting in vitro growth characteristics, can confer a selective advantage under host conditions, allowing the C. glabrata mutant to be more virulent than wild-type isolates.
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